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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,726	11/06/2008	Jack J. Hawiger	21392/1212794-US1	9649

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,726	HAWIGER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *15,26 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 16-25, 27,28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-31* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/09;4/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-28, drawn to an isolated polypeptide, nucleic acid encoding such, vectors, host cells, and methods of administering in the reply filed on 04 September 2009 is acknowledged. Applicant's election without traverse of "infection" as the species of condition associated with inflammation is acknowledged.

Claims 15, 26, 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04 September 2009.

Claims 1-14, 16-25, 27, and 28 are under consideration in the instant application.

Specification

1. The disclosure is objected to because of the following informalities:

1a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. It is not clear is Applicant is attempting to claim priority to the provisional application under 35 U.S.C. § 120 (please see MPEP § 201.11(III)(B)).

Appropriate correction is required.

Claim Objections

2. Claims 3, 10, and 19 are objected to because of the following informalities:

2a. Claim 3 uses the acronym "SOCS" without first defining what it represents in the independent claim. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

2b. In claim 10, line 1, after the phrase "the purification sequence is", the term "a" should be inserted.

2c. In claim 19, lines 1-2, the phrase "staphylococcus enterotoxin B" should be amended to recite "*Staphylococcus enterotoxin B*".

2d. Applicant is advised that should claim14 be found allowable, claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4, 5, 7, 8, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 4 is rejected as being indefinite because it recites the nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 4. Claim 4 depends from claim 3

which requires a nucleic acid sequence encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence. However, SEQ ID NO: 4 is simply the full-length amino acid sequence of SOCS3, with no membrane translocation sequence (see specification page 12, [45]). So, claim 4 does not limit claim 3.

5. Claim 5 is rejected as being indefinite because it recites the nucleic acid sequence comprising the nucleotide sequence set forth in SEQ ID NO: 11. Claim 5 ultimately depends from claim 3 which requires a nucleic acid sequence encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence. However, SEQ ID NO: 11 is simply the full-length nucleotide sequence of SOCS3, with no membrane translocation sequence (see specification pages 12-13, [45]). So, claim 5 does not limit claim 3.

6. Claim 7 is rejected as being indefinite because it is unclear whether open or closed term language is intended (i.e., "containing"). See MPEP § 2111.03.

7. Claim 8 recites the limitation "The composition of claim 1" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1, upon which claim 8 depends, does not recite a composition, but rather an isolated polypeptide. (Please note that this issue could be overcome by amending to claim 8 to recite, for example "The polypeptide of claim 1...".)

8. Claims 12, 13, 14, 16-22 are rejected as being indefinite because it is not clear what the goal of claim 12 is. For example, claim 12, line 1 only recites "A method comprising...". The instant specification teaches that the SOCS sequences may be administered to treat or inhibit inflammation (page 32, [107]). The specification also discloses that the compositions may be administered prophylactically (page 32, [108]). The specification teaches that the compositions

and methods can be used for example as tools to isolate and test new drug candidates for a variety of inflammatory related diseases (page 32, [110]). Also, claim 21, which depends from claim 12, recites that the polypeptide is administered to the subject prior to or after surgery. Claim 22, which depends from claim 12, recites that the polypeptide is administered to the subject prior to or after contact with an infectious biological weapon. Since the specification discloses several methods wherein the SOCS sequences are administered and diverse subject populations encompassed by claims 21 and 22, it is not clear what goal claim 12 is intending to encompass.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 7, 12-14, 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising the vector of claim 6, ***does not reasonably provide enablement for*** a cell containing the vector of claim 6. Furthermore, the specification, while being enabling for a method of reducing inflammation comprising administering a polypeptide comprising a SOCS1 or SOCS3 sequence and a membrane translocation sequence to a subject suffering from inflammation ***does not reasonably provide enablement for*** a method comprising administering a polypeptide comprising a SOCS sequence and a membrane translocation sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is directed to a cell containing a vector comprising the nucleic acid. Claim 12 recites a method comprising administering the polypeptide of claim 1 to a subject. Claim 13 recites that the subject is a subject with inflammation or at risk of inflammation. Claim 16 recites that the inflammation is associated with an infection. Claim 21 recites that the polypeptide is administered prior to or after surgery. Claim 22 recites that the polypeptide is administered to the subject prior to or after contact with an infectious biological weapon.

(i) The Examiner has interpreted the claims as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that the compositions can be administered in a pharmaceutically carrier and can be delivered to the subject's cells in vivo and/or ex vivo by a variety of mechanisms known in the art (page 22, [76]). The specification continues to state that "[t]he compositions can be introduced into the cells via any gene transfer mechanism, such as, for example, calcium phosphate mediated gene delivery, electroporation, microinjection or proteoliposomes (page 22, [76]). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence is demonstrated to express the polypeptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the DNA "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were

unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses one possible technique used to introduce the nucleic acid into animals includes microinjection. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention.

Furthermore, the specification does not teach any methods or working examples that indicate a nucleic acid encoding a SOCS sequence and a membrane translocation sequence is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the nucleic acid into the cell or in what quantity and duration. Relevant literature

teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a nucleic acid in the cell of an organism or be able to produce the protein of interest in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the polypeptide comprising a SOCS sequence and a membrane translocation sequence and to introduce and express the nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding how to introduce the nucleic acid in the cell of an organism to be able produce that polypeptide; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make

and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell…").

(ii) The specification of the instant application teaches that any SOCS protein, such as SOCS-1, SOCS-2, SOCS-3, SOCS-4, SOCS-5, SOCS-6, or SOCS-7, can be used as the source of the SOCS sequence (page 10, lines 28-29). The specification also discloses that recombinant CP-SOCS3 (which includes the 12 amino acid membrane translocating motif) suppresses systemic inflammatory response (pages 49-50, Example 4). The state of the art teaches that expression of SOCS1 or SOCS3 reduce inflammation in several different inflammatory diseases (Alexander et al. Annu Rev Immunol 22: 503-529, 2004; see especially page 519;; cited on the IDS of 28 April 2008; see also Hanada et al. Rev Physiol Biochem Pharmacol 149: 72-86, 2003, especially pages 77-80). However, the specification and the prior art do not teach that any SOCS proteins, other than SOCS1 and SOCS3, play a role in reducing inflammation, as required by the instant claims. Larsen et al. indicate that at the present, there seems to be no clear evidence that the expression of SOCS-4, SOCS-5, SOCS-6, and SOCS-7 mRNAs is induced by cytokines, and very little is known about the function and mechanisms of the actions involved (APMIS 110: 833-844, 2002, cited on the IDS of 28 April 2008;; page 834, column 1). Larsen et al. also teach that studies with SOCS-2 in mice suggest a primary role in regulation of growth by GH and IGF-I (page 841, bottom of column 1). Larsen et al. state that "[e]ven though all the SOCS proteins exhibit a similar structure, with a conserved central SH2 domain and a C-terminal SOCS box, the sequence identity between these members reveals an only distant relationship, reflected by variations in tissue expression, expression kinetics, specificity, and not least the different mechanisms of inhibition" (page 842, column 2). Hence, one skilled in the art would not be able

to predict that all SOCS proteins have a conserved function, or that all SOCS proteins would be able to reduce inflammation in a subject. The specification of the instant application does not teach any methods or working examples that indicate any SOCS, other than SOCS3, reduces inflammation or treats any other diseases or disorders. Due to this lack of guidance, a large quantity of experimentation would be required of the skilled artisan to determine the role of SOCS-2, SOCS-4, , SOCS-5, SOCS-6, and SOCS-7 in inflammation. Such experimentation is considered undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Hilton et al. (U.S. Patent 6,323,317).

Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence alignment attached to the instant Office Action as Appendix A).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 3, 4, 6-12, 23, 27, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilton et al. (U.S. Patent 6,323,317) in view of Lin et al. (WO 99/49879).

Hilton et al. identify a new family of proteins (SOCS) which are capable of acting as regulators of signaling (column 3, lines 27-30). Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence alignment attached to the instant Office Action as Appendix A). Hilton et al. also disclose nucleic acid molecules encoding other members of the SOCS family, as well as the proteins themselves (column 3, lines 58-59; column 7, lines 33-52; column 10, Table 1). Hilton et al. disclose a pharmaceutical composition comprising genetic molecules, such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating SOCS expression or SOCS activity (column 31, lines 65-67 through column 32, lines 1-6).

Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11).

Hilton et al. do not teach a polypeptide comprising a SOCS sequence and a membrane translocation sequence. Hilton et al. do not teach a nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence.

Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell, and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence and a biologically active polypeptide (page 1, 2nd paragraph). Lin et al. disclose that until now, DNA constructs, including DNA vaccines and recombinant viral vectors, have provided the most effective method for furnishing a protein product to the cell for processing and expression (page 2, line 32 through page 3, lines 1-3). Lin et al. add that the FDA has expressed concern about approval of DNA vaccines and that recombinant viral vectors have posed problems in terms of delivery into cells, efficiency of expression, and potential immune system response to viral proteins (page 3, lines 4-11). Lin et al. indicate that there is need for a method for importing entire protein molecules into a cell for studies of intracellular processes in living systems, for drug delivery, for vaccine development, and for disease therapy (page 3, lines 22-25). Lin et al. teach an artificial MTS sequence of 12 amino acids (and DNA encoding such) that can be used as a fusion with a target protein for import into the cell (page 7, lines 23-29). The MTS of Lin et al. is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see page 7, lines 31-32 of Lin et al.; SEQ ID NO: 1 of Lin et al.). Lin et al. disclose that an

expression vector comprising the MTS and the target protein may also encode a polyhistidine (6xHis) sequence and an epitope tag to allow rapid purification of the fusion protein (page 13, lines 29 through page 14, lines 1-5).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the SOCS amino acid sequences (and nucleic acid sequences encoding such) of Hilton et al. by fusing them to a membrane translocation sequence as taught by Lin et al. The person of ordinary skill in the art would have been motivated to make that modification because (i) SOCS proteins are *intracellular* regulators of cell signaling, wherein modulation of SOCS activity or expression requires administration of agonists, antagonists, or DNA constructs as taught by Hilton et al. and (2) problems with DNA constructs (i.e., gene therapy and recombinant viral vectors) were known in the art at the time the invention was made (see Lin et al. page 3, lines 4-11). The person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also, pages 35-37). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

13. Claims 12, 13, 14, 20, 23, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shouda et al. (J Clin Invest 108(12): 1781-1788, 2001) in view of Hilton et al. (U.S. Patent 6,323,317) and Lin et al. (WO 99/49879).

Shouda et al. teach that the mRNA of SOCS3 (CIS3) is abundantly expressed in patients with rheumatoid arthritis, an autoimmune disease characterized by chronic inflammation of the joints (abstract; page 1783, column 2; page 1784, column 1). Shouda et al. teach that the

administration of a recombinant adenovirus carrying SOCS3 cDNA is injected into the ankle joints of mice with antigen-induced arthritis or collagen-induced arthritis (abstract; bottom of page 1784, column 2; page 1785 through page 1786). Shouda et al. disclose that the SOCS3 adenovirus drastically reduced the severity of arthritis and joint swelling as compared to controls (abstract; Figures 5, 6; page 1787, column 1, second full paragraph). Shouda et al. conclude that adenovirus-mediated gene transfer of the SOCS3 gene is a promising means of treatment for rheumatoid arthritis (abstract; page 1788, top of column 1).

Shouda et al. do not teach the administration of a polypeptide comprising a SOCS sequence and a membrane translocation sequence.

Hilton et al. identify a new family of proteins (SOCS) which are capable of acting as regulators of signaling (column 3, lines 27-30). Hilton et al. teach an isolated nucleic acid sequence that encodes the SOCS3 amino acid sequence of SEQ ID NO: 4 of the instant application (see nucleic acids 18-692 of SEQ ID NO:7 of Hilton et al.; see also sequence alignment attached to the instant Office Action as Appendix A). Hilton et al. also disclose nucleic acid molecules encoding other members of the SOCS family, as well as the proteins themselves (column 3, lines 58-59; column 7, lines 33-52; column 10, Table 1). Hilton et al. disclose a pharmaceutical composition comprising genetic molecules, such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating SOCS expression or SOCS activity (column 31, lines 65-67 through column 32, lines 1-6). Hilton et al. teach the use of SOCS or its functional derivatives in the manufacture of a medicament for the treatment of conditions involving cytokine mediated cellular responsiveness (column 36, lines 8-11).

Lin et al. teach a membrane translocating sequence (MTS) for directing import of biologically active protein molecules into a cell, and a method of using an expression vector in a host cell to produce a fusion protein comprising a membrane-translocating sequence and a biologically active polypeptide (page 1, 2nd paragraph). Lin et al. disclose that until now, DNA constructs, including DNA vaccines and recombinant viral vectors, have provided the most effective method for furnishing a protein product to the cell for processing and expression (page 2, line 32 through page 3, lines 1-3). Lin et al. add that the FDA has expressed concern about approval of DNA vaccines and that recombinant viral vectors have posed problems in terms of delivery into cells, efficiency of expression, and potential immune system response to viral proteins (page 3, lines 4-11). Lin et al. indicate that there is need for a method for importing entire protein molecules into a cell for studies of intracellular processes in living systems, for drug delivery, for vaccine development, and for disease therapy (page 3, lines 22-25). Lin et al. teach an artificial MTS sequence of 12 amino acids (and DNA encoding such) that can be used as a fusion with a target protein for import into the cell (page 7, lines 23-29). The MTS of Lin et al. is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see page 7, lines 31-32 of Lin et al.; SEQ ID NO: 1 of Lin et al.). Lin et al. disclose that an expression vector comprising the MTS and the target protein may also encode a polyhistidine (6xHis) sequence and an epitope tag to allow rapid purification of the fusion protein (page 13, lines 29 through page 14, lines 1-5).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating rheumatoid arthritis of Shouda et al. by substituting the recombinant adenovirus carrying SOCS3 cDNA for a fusion polypeptide

comprising SOCS3 and a membrane translocation sequence as taught by Hilton et al. and Lin et al. The person of ordinary skill in the art would have been motivated to make that modification because problems with DNA constructs (i.e., gene therapy and recombinant viral vectors) were known in the art at the time the invention was made (see Lin et al. page 3, lines 4-11). The person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also, pages 35-37). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
23 December 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Appendix A

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US-09-302-769-7
; Sequence 7, Application US/09302769
; Patent No. 6323317
; GENERAL INFORMATION:
;  APPLICANT:  HILTON, Douglas J
;  APPLICANT:  ALEXANDER, Warren S
;  APPLICANT:  VINEY, Elizabeth M
;  APPLICANT:  WILLSON, Tracey A
;  APPLICANT:  RICHARDSON, Rachael T
;  APPLICANT:  STARR, Robyn
;  APPLICANT:  NICHOLSON, Sandra E
;  APPLICANT:  METCALF, Donald
;  APPLICANT:  NICOLA, Nicos A
;  TITLE OF INVENTION:  THERAPEUTIC AND DIAGNOSTIC AGENTS
;  FILE REFERENCE:  10976Z
;  CURRENT APPLICATION NUMBER: US/09/302,769
;  CURRENT FILING DATE:  1999-04-30
;  PRIOR APPLICATION NUMBER:  08/962,560
;  PRIOR FILING DATE:  1997-10-31
;  NUMBER OF SEQ ID NOS:  50
;  SOFTWARE:  PatentIn Ver. 2.0
; SEQ ID NO 7
;   LENGTH: 2187
;   TYPE: DNA
;   ORGANISM: Mouse
;   FEATURE:
;   NAME/KEY: CDS
;   LOCATION: (18)..(692)
US-09-302-769-7

Alignment Scores:
Length:                 2187
Score:                  1177.00       Matches:       225
Percent Similarity:     100.0%        Conservative:  0
Best Local Similarity:  100.0%        Mismatches:    0
Query Match:            100.0%        Indels:        0
DB:                     3             Gaps:          0

US-10-589-726-4 (1-225) x US-09-302-769-7 (1-2187)

Qy          1 MetValThrHisSerLysProAlaAlaGlyMetSerArgProLeuAspThrSerLeu 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         18 ATGGTCACCCACAGCAAGTTTCCCGCCGCCGGGATGAGCCGCCCCCTGGACACCAGCCTG 77

Qy         21 ArgLeuLysThrPheSerSerLysSerGluTyrGlnLeuValValAsnAlaValArgLys 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         78 CGCCTCAAGACCTTCAGCTCCAAAAGCGAGTACCAGCTGGTGGTGAACGCCGTGCGCAAG 137

Qy         41 LeuGlnGluSerGlyPheTyrTrpSerAlaValThrGlyGlyGluAlaAsnLeuLeuLeu 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        138 CTGCAGGAGAGCGGATTCTACTGGAGCGCCGTGACCGGCGGCGAGGCGAACCTGCTGCTC 197

Qy         61 SerAlaGluProAlaGlyThrPheLeuIleArgAspSerSerAspGlnArgHisPhePhe 80
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        198 AGCGCCGAGCCCGCGGGCACCTTTCTTATCCGCGACAGCTCGGACCAGCGCCACTTCTTC 257

Qy         81 ThrLeuSerValLysThrGlnSerGlyThrLysAsnLeuArgIleGlnCysGluGlyGly 100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        258 ACGTTGAGCGTCAAGACCCAGTCGGGGACCAAGAACCTACGCATCCAGTGTGAGGGGGGC 317

Qy        101 SerPheSerLeuGlnSerAspProArgSerThrGlnProValProArgPheAspCysVal 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        318 AGCTTTTCGCTGCAGAGTGACCCCCGAAGCACGCAGCCAGTTCCCCGCTTCGACTGTGTA 377
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Qy        121 LeuLysLeuValHisHisTyrMetProProProGlyThrProSerPheSerLeuProPro 140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        378 CTCAAGCTGGTGCACCACTACATGCCGCCTCCAGGGACCCCCTCCTTTTCTTTGCCACCC 437

Qy        141 ThrGluProSerSerGluValProGluGlnProProAlaGlnAlaLeuProGlySerThr 160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        438 ACGGAACCCTCGTCCGAAGTTCCGGAGCAGCCACCTGCCCAGGCACTCCCCGGGAGTACC 497

Qy        161 ProLysArgAlaTyrTyrIleTyrSerGlyGlyGluLysIleProLeuValLeuSerArg 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        498 CCCAAGAGAGCTTACTACATCTATTCTGGGGGCGAGAAGATTCCGCTGGTACTGAGCCGA 557

Qy        181 ProLeuSerSerAsnValAlaThrLeuGlnHisLeuCysArgLysThrValAsnGlyHis 200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        558 CCTCTCTCCTCCAACGTGGCCACCCTCCAGCATCTTTGTCGGAAGACTGTCAACGGCCAC 617

Qy        201 LeuAspSerTyrGluLysValThrGlnLeuProGlyProIleArgGluPheLeuAspGln 220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        618 CTGGACTCCTATGAGAAAGTGACCCAGCTGCCTGGACCCATTCGGGAGTTCCTGGATCAG 677

Qy        221 TyrAspAlaProLeu 225
              |||||||||||||||
Db        678 TATGATGCTCCACTT 692
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